Appendix B

I hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, DC 20231, on the date listed below.

Signature

18 Nov 96

Date

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXAMINER:	R. ROSENBERGER	: ATTY DOCKET NO.:	GK-BIO-292C2
APPLICANT(S):	E. W. STARK	: GROUP ART UNIT:	2505
SERIAL NO.:	08/385,073	: FILED:	02/07/95

TITLE: METHOD AND APPARATUS FOR OPTICAL INTERACTANCE AND TRANSMITTANCE MEASUREMENTS

---oOo---

BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

RECEIVED
JAN 14 1997
GROUP 2500

TRANSMITTAL LETTER

SIR:

Transmitted herewith is an Amendment, A Petition for a Three Month Extension-of-Time, and a Notice of Appeal for the above-identified application.

	CLAIMS REMAINING AFTER RESPONSE	NUMBER OF PREVIOUSLY PAID CLAIMS	# OF EXTRA CLAIMS	RATE	FEE
TOTAL	38	43	0	$22	$0
INDEPENDENT	13	13	0	$80	$0
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIMS			0	$260	$0
FEES REQUIRED FOR AN EXTENSION-OF-TIME AND A NOTICE OF APPEAL					$1,230
TOTAL FEE FOR THIS RESPONSE					$1,230

__X__ A check covering the total fee amount indicated above is attached.

__X__ The period of response for the outstanding Office Action has been extended to November 18, 1996, as requested in a Petition submitted herewith.

__X__ The Commissioner is hereby authorized to charge any additional fees included in 37 CFR §§ 1.16 and 1.17 which may be required, or credit any overpayment to Account No. 13-0025.

Respectfully submitted,
McAULAY FISHER NISSEN GOLDBERG & KIEL, LLP

Gerald H. Kiel

Gerald H. Kiel
Reg. Number: 25,116
Telephone: 212-986-4090
Facsimile: 212-818-9479

MC AULAY FISHER NISSEN
GOLDBERG & KIEL, LLP

DATE : Oct 31, 1996
CHE # : 19461
AMOUNT: $1,230.00
COMM. EXT. OF TIME AND NOTICE OF APPEAL
MATTER: 4025
CLIENT: 366 - Mr. Edward Stark

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GROUP 2500

1946

MC AULAY FISHER NISSEN
GOLDBERG & KIEL, LLP
261 MADISON AVENUE NY, NY 10016

STERLING NATIONAL BANK
& TRUST COMPANY OF NEW YORK
NEW YORK, NY 10022
1-777-260

Oct 31, 1996 DATE $1,230.00 AMOUNT

One Thousand Two Hundred Thirty ************************************** 00/100

PAY TO THE ORDER OF Assistant Commissioner for Patents

⑈019461⑈ ⑆026007773⑆ 38 000532⑈01

I hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, DC 20231, on the date listed below.

Signature: Ruth Matlack   Date: 18 Nov 96

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXAMINER:	R. ROSENBERGER	: ATTY DOCKET NO.:	GK-BIO-292C2
APPLICANT(S):	E. W. STARK	: GROUP ART UNIT:	2505
SERIAL NO.:	08/385,073	: FILED:	02/07/95
TITLE:	METHOD AND APPARATUS FOR OPTICAL INTERACTANCE AND TRANSMITTANCE MEASUREMENTS		

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BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT UNDER 37 CFR §1.116

SIR:

In response to a Final Office Action dated May 16, 1996, which has a period for response that has been extended to November 18, 1996, by payment of appropriate fees, please amend the above-identified application as follows.

IN THE SPECIFICATION:

Page 4, line 27 replace "of quantitative" with --or quantitative--.

IN THE CLAIMS:

Please **AMEND** claim 55 as follows.

Claim 55. (Once Amended) A method for the non-invasive measurement of a substance in living tissue comprising:

contacting a patient with [an] said emitter means and [a] said first and second radiation detection means of said apparatus of claim 54;

emitting electromagnetic radiation through said emitter means into said patient;

detecting electromagnetic radiation which has been scattered and attenuated by said patient with said first and second radiation detection means; and

producing a quantitative measure of said substance in said living tissue by determining the ratio of the intensities of said electromagnetic radiation detected by said first and second radiation detection means.

REMARKS

I) INTRODUCTION

Claims 1, 6-7, 11-15, 17-19, 22-26, 33-43, and 45-55 are now pending in the application. Claims 1, 6-7, 33-34 and 36-42 stand rejected under 35 USC § 103, claims 11-15, 17-19, 22-26, 35, 43 and 45-53 stand allowed, and claims 54-55 stand rejected under 35 USC §§ 112 and 102. The foregoing amendments and following remarks are considered by applicant overcome each of the outstanding rejections.

The Examiner is now respectfully requested by applicant to take ***two*** specific actions regarding the examination of this application. First, the Examiner is requested to withdraw each of his outstanding rejections and allow all of the claims currently pending in the application. Second, the Examiner is requested to declare an interference proceeding between claims 54-55 of the current application and US Patent 5,419,321 issued to Evans. Newly presented evidence and arguments in support of these two requests are presented below.

II) OUTSTANDING REJECTIONS

In paragraph 1 of the Office Action, the Examiner has rejected claims 54 and 55 under 35 USC § 112, first paragraph, on the basis that the claims are not supported by the specification as originally filed. In particular, the Examiner contends that the specification as originally filed does not support the language used in claims 54 and 55 relating to "living tissue" of a "patient." This rejection is respectfully traversed and believed overcome in view of the following two arguments.

First, contrary to the Examiner's position, the text "the layers of skin and fat which cover muscle tissue" on page 1, lines 22-23 of the specification does indeed encompass the "living tissue" of a "patient." This interpretation is not only supported by the direct language of the specification but is additionally supported by language contained in an article, "A New Approach to the Estimation of Body Composition: Infrared Interactance," which is cited on page 2, lines 28-31, of the specification.

Second, it is well settled that to comply with the requirements of the first paragraph of 35 USC § 112, the specification need not describe ***verbatim*** the subject matter of claims 54 and 55. So long as the specification clearly conveys to those skilled in the art information sufficient to establish inventorship in the subject matter identified in the claims, the specification will be considered to comply with this provision of US patent law. It is clear that the specification of the current application, taking into account all the information cited above, meets this standard.

For these two reasons, applicant considers claims 54 and 55 to be fully compliant with the requirements of the first paragraph of 35 USC § 112. The Examiner is therefore respectfully requested to withdraw this rejection.

In paragraph 3 of the Office Action, the Examiner has rejected claims 54 and 55 under 35 USC §102(e) as being anticipated by US Patent 5,057,695 (Hirao). This rejection is respectfully traversed by applicant and believed overcome in view of the following arguments.

Applicant respectfully points out to the Examiner that rejected claims 54 and 55, as amended and presented above, are identical to claims 1 and 2 of US Patent 5,419,321 issued to Evans. As is clearly indicated on the cover page of Evans, claims 1 and 2 recited therein have previously been found by the USPTO to be patentable over Hirao. It is therefore axiomatic that claims 54 and 55 of the present application carry the same legal presumption of validity over Hirao as do clams 1 and 2 of Evans.

Notwithstanding the foregoing, in Appendix 1 of this Amendment, applicant has provided the Examiner with a Declaration under 37 CFR §1.131. This Declaration presents evidence which establishes that Hirao does not qualify as prior art against the subject invention. Thus, in view of this Declaration, the Examiner will now be required to withdraw his outstanding anticipation rejection of claims 54 and 55.

In paragraph 5 of the Office Action, the Examiner rejects claims 1, 6, 7, 33, 34, and 36-42 under 35 USC § 103 as being unpatentable over the prior art discussed on pages 2-4 of the specification and US Patent 4,884,891 (Borsboom) in view of US Patent 3,994,602 (Howarth) and US Patent 5,057,695 (Hirao). In response to this rejection, applicant refers the Examiner to additional Declarations which are submitted under 37 CFR §1.132 and included in Appendices 2-3 of this Amendment. The Examiner's rejection is respectfully traversed and believed overcome in view of each of the attached Declarations.

As a preliminary matter, applicant again points out that the Declaration provided in Appendix 1, which was filed under 37 CFR §1.131, establishes that Hirao does not qualify as prior art against the rejected claims. Thus, the Examiner's obviousness rejection recited in paragraph 5 of the Office Action must now be withdrawn given that it was, in part, based on this reference.

Applicant has, nevertheless, submitted a second and third Declaration to provide the Examiner with further evidence establishing that the claimed invention is nonobvious over the cited references. These two Declarations are discussed in detail below.

The second Declaration, which is provided in Appendix 2 of this Amendment, was prepared by Dr. Harry Shamoon. This second Declaration presents evidence which establishes, among other things, that: (i) there has been a long felt need for a device which could accurately and noninvasively measure the blood glucose of a patient, and (ii) applicant's claimed invention solves this longstanding problem by providing unexpectedly beneficial measurements over the prior art devices.

Specifically, the evidence in Section IV of Dr. Shamoon's Declaration establishes that a previous study by the NIDDK demonstrates that by properly controlling blood glucose levels, the incidence of various complications of diabetes could be reduced by 42% to 76%. This section of the Declaration further establishes that a long felt need exists for a noninvasive blood glucose measuring device, where 95% of the results from such a device would fall within +/- 20% of the true value.

Also, the evidence in Sections V and VI of Dr. Shamoon's Declaration summarizes tests performed with both prior art single-ring devices and applicant's dual-ring device. Figures 5-6, which are described in these Sections, specifically show the results of the tests performed with the prior art single-ring devices. Figure 4, which is also described in these Sections, shows the results of tests performed with applicant's claimed dual-ring device. A comparison of these charts shows that when applicant's claimed dual-ring device is used, a significantly smaller number of measurements fall outside the +/- 20% error margin.

The third Declaration, which is provided in Appendix 3 of this Amendment, was prepared by Karl Norris who previously held the position of Director at the USDA's Agricultural Research Service Instrumentation Research Laboratory. Mr. Norris' Declaration further establishes: (i) the closest prior art in the field; (ii) that a long-standing problem existed in the prior art devices, and (iii) that applicant's claimed invention provides an unexpected beneficial solution to these problems.

First, evidence in Section III of the Norris Declaration establishes that the closest prior art devices in the field are fiber optic probes. These devices all use a single source and a single detection means. Prior art devices, such as these, have presented a long-standing problem in that they do not provide accurate measurements when the surface portion of the sample being tested is different from a deeper interior portion of the sample. In particular, these devices do not obtain two measurements of information to discriminate between regions near the surface of the sample and regions in the interior portion of the sample. This distinction is critical when the measurement of interest relates to the interior of the sample and the surface effects may be variable.

Norris further points out that, while these prior art devices may maximize the measurement volume, they do not optimize it because, among other reasons, the depth of penetration and pathlength vary simultaneously with the spacing between the source and detection means and the region near the central aperture is unduly weighted in the measurement.

Evidence in Section III of the Norris Declaration further reviews Borsboom, Hirao and Howarth in the context of the closest prior art in the field. Borsboom, according to the Norris Declaration, appears to combine a reflectometer to measure backscatter with a single ring interactance probe to measure absorption. However, Borsboom does not disclose the combining of the two measurements which will be required to solve the longstanding problem in the art discussed above. He also provides no teaching on the advantages of a full ring over his suggested

alternative use of on or four fibers.

Hirao, although not prior art, was also discussed in the Norris Declaration. According to Norris, Hirao uses a linear arrangement of a source and detection apertures to provide two optical paths. Hirao, however, does not appreciate the importance of the depth of penetration differences between the two paths. Hirao's concern is to minimize the inhomogeneity within the measurement volume to improve the reproducibility of the results. He therefore wishes to define a small measurement region by the difference between the two paths. In order to maximize the commonality of path to ensure cancellation of the common signal, and to avoid surface affects which are present near the common aperture, Hirao creates two paths whose length is much greater than the space between their end points. Hirao therefore teaches away from the use of extended apertures which would increase the size of his measurement region.

Howarth, according to the Norris Declaration, uses only one source and detection aperture for measurement of "bulk reflectance." Howarth shows that the detection window spacing should be sufficiently large so that most of the optical photon paths lie outside the boundary layer. However, contrary to the Examiner's statement on page 9 of the Office Action, Norris establishes that Howarth's "apertures are made fully diffusing so that there is no optical directionality of the light within the sample caused by the angle at which the sources or detectors are placed relative to the window." The major portion of Howarth's disclosure describes a very simple form of the prior art interactance measurement technique which provides no improvement in combination with Borsboom or the other prior art cited by applicant.

Norris indicates that the "consistency" measurement, for which Howarth does disclose a linear arrangement of a source and two detection windows, is based only on scattering and not absorption and that, in order to optimize the consistency measurement, Howarth uses a window spacing which would decrease the accuracy and precision of the bulk reflectance measurement, which depends on absorption. The only problems that Howarth defines for this scattering measurement are pitch and dirt on the windows and pulp noise. He does not suggest using two detection windows for his absorption (interactance) measurement of bulk reflectance even though he cites "it is another object of the invention to provide a gauge as above which is less sensitive to fouling of the window through which measurements are being made and also to boundary layer effects." Moreover, in his disclosure "to measure the ratio of received radiation in at least two different window locations," Howarth simply does not address the depth of penetration of the optical paths, problems of layered inhomogeneous samples, optimizing measurement volume, nonlinearity, or the other aspects of optimizing a multiple path <u>interactance</u> measurement which are considered by applicant.

Norris concludes that "...Borsboom does no more than disclose the basic interactance optical geometry..." and "...neither Hirao nor Howarth disclose any teaching which would lead an individual skilled in the art to the invention made by applicant."

In view of the foregoing, Section III of the Norris Declaration clearly establishes that the closest prior art known to the claimed invention, including Borsboom, Hirao, and Howarth, to the extent that these references qualify as prior art, simply did not appreciate the problem which applicant's claimed invention solves.

Second, evidence in Section IV of the Norris Declaration establishes that there has been a long-felt need for a device that would overcome the problems with the prior art devices discussed above. To reduce the effects of sample inhomogeneity, the improved device would maximize the measurement volume for a predetermined spacing and avoid preferentially measuring any region of the sample, control the effective depth from which the measurement was made in order to measure the desired stratum within the sample while reducing surface effects, define and limit the effective optical paths to reduce nonlinearity, and maximize the signal-to-noise ratio of the measurement.

Third, evidence in Section V of the Norris Declaration establishes that applicant's claimed invention provides a significant and unexpected improvement over the prior art devices described above. Norris believes that applicant's invention meets the above device criteria for fulfilling the long-felt need. In particular, this section of the Declaration verifies the findings of Dr. Shamoon, and further establishes that the measurements produced by applicant's claimed invention are both superior and unexpected as compared to the prior art devices. This section of the Norris Declaration also establishes, contrary to the Examiner's statements in the third full paragraph on page 9 of the Office Action, that the geometry of the light source and detectors in applicant's claimed invention, is of functional importance.

In view of the objective evidence presented in the Declarations described above, applicant has (i) established that Hirao does not qualify as prior art against the subject application, and (ii) established that rejected claims 1, 6-7, 33-34 and 36-42 are nonobvious as compared to the cited references. The Examiner is therefore requested to withdraw his outstanding rejection under 35 USC § 103 and allow these claims based on this evidence.

III) DECLARATION OF AN INTERFERENCE

In paragraph 6 of the Office Action, the Examiner states that the interference requested in applicant's Amendment dated December 5, 1996, is not being declared. The basis for the Examiner's position is that he does not consider the interfering subject matter - claims 54 and 55 - to be patentable over Hirao. As explained above, the USPTO has previously found claims containing the same language as claims 54 and 55 to be patentably distinct from Hirao and, moreover, Hirao does not qualify as prior art against this application. The Examiner is therefore requested to reconsider this decision and declare an interference proceeding.

In paragraph 7 of the Office Action, the Examiner contends that claim 55 does not correspond substantially to claim 2 in the Evans patent as applicant previously asserted in his Amendment filed on December 5, 1995. Specifically, the Examiner contends that claim 55 is broader than claim 2 given that claim 55 does not include a limitation which requires the first and second detection means to be spaced at different distances from the emitter means. In response to the Examiner's suggestion, claim 55 has been amended such that it is now ***identical*** to claim 2 of Evans.

IV) ALLOWED CLAIMS

In paragraph 8 of the Office Action, the Examiner again indicates that claims 11-15, 17-19, 22-26, 35 and 53 are allowable. Additionally, in paragraph 9 of the Office Action, the Examiner indicates that claims 43 and claims 45-52 have also been allowed as a result of the Amendment we previously filed on November 10, 1995. Applicant thanks the Examiner for confirming the allowability of these claims.

V) CONCLUSION

In view of the foregoing discussion, the Examiner is now requested to (i) allow all of the claims currently pending in the application and (ii) declare an interference proceeding between claims 54-55 of the current application and US Patent 5,419,321 issued to Evans. A communication from the Examiner granting these two requests is earnestly solicited.

Respectfully submitted,
McAULAY FISHER NISSEN GOLDBERG & KIEL, LLP

Gerald H. Kiel

Gerald H. Kiel
Reg. Number: 25,116
Telephone: 212-986-4090
Facsimile: 212-818-9479

Exhibit 1

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXAMINER:	R. ROSENBERGER	: ATTY DOCKET:	GK-BIO-282C2
APPLICANT(S):	E. W. STARK	: GROUP ART UNIT:	2505
SERIAL NO.:	08/385,073	: FILED:	02/07/95
TITLE:	METHOD AND APPARATUS FOR OPTICAL INTERACTANCE AND TRANSMITTANCE MEASUREMENTS		

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Assistant Commissioner for Patents
Washington, D.C. 20231

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JAN 14 1997
GROUP 2500

DECLARATION UNDER 37 CFR §1.131

SIR:

I Karl Norris hereby declare the following:

I

I have been educated as an agricultural engineer having received my Bachelor of Science in Engineering from Penn State University in 1942. Since graduation, among other endeavors, I have been involved in research involving measurements of specimens using infrared illumination. I was co-author of a paper published in 1984 entitled "A New Approach for the Estimation of Body Composition: Infrared Interactance," American Journal of Clinical Nutrition, Vol. 40, pp 1123-1130. I was also the Director of the USDA Agricultural Research Service Instrumentation Research Laboratory in Beltsville, MD until I retired in 1988. I make this Declaration in support of the above application of Mr. Edward Stark.

II

During a period prior to December 15, 1989, I was in direct contact with Edward Stark and we discussed numerous matters involving measurements of specimens illuminated by electromagnetic energy. Mr. Stark informed me during that period about a new invention of his for interactance measurements of specimens using a multiple ring probe arrangement. The first version contained multiple detection and source rings allowing flexible configuration of the interactance measurement. The dual ring arrangement had either a central source of illumination with surrounding detector rings or outer rings of illumination with a central detector. The principal purpose of the probe was to develop two or more independent signals of a sample, particularly for interactance measurements, for further processing and analysis.

III

During a period prior to December 15, 1989, I witnessed several sketches of the dual ring and probe and also traveled with Mr. Stark to Fostek, Inc., and Volpi Manufacturing USA, both in Auburn, NY where Mr. Stark explained his invention to others.

I, Karl Norris, hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Karl H. Norris
Signature of Declarant

Nov. 17, 1996
Date

Exhibit 2

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXAMINER:	R. ROSENBERGER	: ATTY DOCKET:	GK-BIO-292C2
APPLICANT(S):	E.W. STARK	: GROUP ART UNIT:	2505
SERIAL NO.:	08/385,073	: FILED	02/07/95
TITLE:	METHOD AND APPARATUS FOR OPTICAL INTERACTANCE AND TRANSMITTANCE MEASUREMENTS		

---oOo---

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132

SIR:

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I, Harry Shamoon, MD, hereby declare the following:

I

I have received the Bachelor of Arts Magna Cum Laude from Columbia College in 1970, and the Doctor of Medicine from the Yale University School of Medicine in 1974. Internship and Residency at the Bronx Municipal Hospital, Albert Einstein College of Medicine occupied me from 1974 to 1977. I was a postdoctoral fellow at the Endocrine section of the Yale University School of Medicine from 1977 to 1979. I am a Diplomate of the National Board of Medical Examiners and the American Board of Internal Medicine with certification in Endocrinology and Metabolism.

II

I have been employed by the Department of Medicine, Division of Endocrinology and Metabolism, Albert Einstein College of Medicine since 1979, most recently as Professor of Medicine and Director, Model Demonstration Unit, Einstein Diabetes Research and Training Center. Since 1980 I have been engaged in research in the field of diabetes with funding from the American Diabetes Association (ADA) and the National Institutes of Health (NIH). I am currently a principal investigator on the Epidemiology of Diabetes Interventions and Complications (follow-up of the Diabetes Control and Complications Trial cohort) and the Diabetes Prevention Program (NIDDM Prevention Trial).

III

I am familiar with prior art devices which perform measurements of blood glucose for the management of diabetes, and with the problems and shortcomings of the prior devices. All of the

medically accepted prior devices require the invasive acquisition of a blood sample in order to make the determination. The need for a painful skin puncture causes many patients to resist testing as frequently as is medically desirable and there is a significant risk of infection when devices are used by multiple individuals. In addition, simple, low cost glucose meters using reagent strips have been shown to be less accurate than desirable when used by the typical patient. Recently a non-invasive glucose measurement device based on near-infrared reflectance was submitted for approval by the U.S. Food and Drug Administration however it was rejected because the data indicated that the accuracy was insufficient.

IV

There has been a long felt need for a device which could make accurate in-vivo, non-invasive measurements of blood glucose for the improved management of diabetes. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored the 10 year long Diabetes Control and Complications Trial which demonstrated that tight control of blood glucose levels could reduce the incidence of various complications of diabetes by 42% to 76% depending on the complication. The Food and Drug Administration has recognized the importance and value of in- vivo, non-invasive blood glucose measurements and indicated the need for accuracy such that 95% of the results fall within +/-20% of the true value. The medical, quality of life and economic benefits of such a device would be of inestimable value.

V

I have carefully reviewed the previous series of tests conducted by Dr. Michael Berelowitz at the State University of New York at Stony Brook using the device described and shown in US Patent Application No. 08/385,073. The clinical tests conducted with the device involved five volunteer normal subjects. The blood glucose level of each subject was increased from the fasting level by intravenous introduction of glucose. The above device was used at frequent intervals to obtain non-invasive in-vivo measurements of the subcutaneous interactance spectrum of the thumb in the visible and near-infrared spectral regions from 400 to 1700 nm wavelength. Simultaneously, blood samples were drawn and the glucose concentration determined by a standard laboratory instrument. These data were then used to generate chemometric calibrations relating the spectral data to the measured blood glucose levels using the partial least squares (PLS) method. The performance of these calibrations were validated by the method of cross-validation whereby the blood glucose level of each sample is predicted from the spectral data using a calibration developed not including that sample's spectral data. A total of approximately 500 spectral data runs consisting of over 1000 spectra each were collected during these tests.

I have also conducted and supervised tests on two subjects at the Albert Einstein College of Medicine utilizing the above device and improved control of the position and pressure applied to the thumb. The first subject was a Type I diabetic whose blood glucose level was normalized at the beginning of the protocol and then reduced from normal to a hypoglycemic state by controlled administration of insulin and glucose. After 6 1/2 hours the blood glucose was rapidly raised to

approximately 150 mg/dl by intravenous introduction of glucose. Non-invasive, in-vivo visible and near-infrared interactance spectra were obtained on the thumb using the above device. Sets of spectral data were collected at intervals of 2.5 minutes, each set consisting of 1200 spectra measured over a 40 second time span. The blood plasma glucose was accurately determined in triplicate every 5 minutes by a standard laboratory instrument. Approximately 150 sets of data were obtained covering the critical low blood glucose situation. Again, these data were used to generate chemometric calibrations by PLS and the predictive performance was determined by cross- validation.

The second subject was a normal individual whose blood glucose was at the fasting level at the beginning of the protocol. In order to avoid introduction of exogenous glucose, the subject ate a breakfast and a lunch to elevate the blood glucose. Noninvasive, in-vivo visible and near-infrared interactance spectra were obtained from the thumb using the above device. Sets of spectral data were collected at intervals of 2.5 minutes, each set consisting of 1200 spectra measured over a 40 second time span. The blood plasma glucose was accurately determined in triplicate every 5 minutes by a standard laboratory instrument. After approximately 45 minutes of fasting data, the subject ate breakfast and then, after 4.5 hours, lunch. Due to an instrument misadjustment, only 58 of the 143 sets of data collected were usable. Therefore, these data were combined with the data from the first subject and used to generate chemometric calibrations by PLS. The predictive performance was determined by cross-validation.

VI

The results of the tests performed with the device are shown below in Figures 1 thru 7 and their interpretation and significance are briefly discussed.

The first four protocols run at Stony Brook, which covered the blood glucose range from approximately 100 to 360 mg/dl, were encouraging but they demonstrated the need for more sets of spectral data from each protocol to adequately support the PLS chemometric calibration process. The fifth protocol (patient: Steven), which covered a blood glucose range of 53 to 315 mg/dl, was extended to over 8 hours in order to obtain more than 200 sets of spectral data for analysis (figure 1). A root mean square difference (RMSD) of 17.5 mg/dl was obtained. These data (figure 2) clearly indicate that the device can provide sufficient accuracy in the above-normal glucose range but improvement was needed in the critical range below 100 mg/dl.

The first protocol run at Einstein (patient: Annmarie) lasted 6 1/2 hours covering the blood glucose range from 53 to 118 mg/dl. Three additional plasma glucose determinations were made at 15 minute intervals after introduction of a bolus of intravenous glucose. The results (figure 3) prior to introduction of the bolus of glucose clearly meet the objective of 95% of the data being within +/- 20% of the reference value. An RMSD of 6.65 mg/dl was obtained. Eight outlier detected by spectral analysis prior to calibration were rejected (o's in figure 4). In practice, the instrument would automatically detect and not report values for these rejected data. The patient would be requested to make another determination.

An unexpected result occurred after the bolus of glucose was injected. The NIR blood glucose predictions remained in the 50-60 mg/dl range (▪'s in figure 4) for nearly an hour although the blood plasma glucose increased very rapidly. These data were eliminated from the calibration that is used for prediction as they were clearly anomalies in the data set. The delay in the response to increased plasma glucose is unexpectedly long. Based on the quality of the earlier results, it is believed that there is probably a physiological basis for this discrepancy rather than any error in the NIR data although the exact mechanism is presently unknown. The NIR determinations reported here are based on the correlation of blood plasma glucose values with spectral data obtained from all the tissue in the optical path, including interstitial fluid and cells. These data suggest that an important delay in tissue glucose levels may go undetected by conventional blood testing methods. Thus NIR determinations using this device may provide additional insight into the kinetics of glucose transport and utilization in the body. Further studies are being conducted to evaluate the mechanism and medical value of this phenomenon.

Using the data from this first protocol, a comparison was made between the dual-ring device that is the subject of the present patent application and the prior-art single-ring devices by using the signal from only one source ring for calibration and cross-validation. Calibration using the inner ring as the source and central detection resulted in an RMSD of 7.11 while using the outer ring as the source and central detection produced an RMSD of 7.89 compared with the dual-ring RMSD of 6.65, a 7% and 19% degradation respectively. The prediction data from the inner ring only (figure 5) and the outer ring only (figure 6) compared to that of the dual-ring device (figure 3) show a significant increase in the number of measurements falling outside +/-20% error, particularly in the most critical low blood glucose range.

The second protocol run at Einstein (patient: David) lasted 6 hours covering the blood glucose range from 87 to 148 mg/dl. The results of the combined data from the first and second protocols (figure 7) show that only 5 of the 177 data points used exceed +/- 20% error, over 97% falling within these limits. An RMSD of 8.22 mg/dl was obtained. Based on spectral analysis, five outliers (o's in figure 8) were eliminated from the second data set prior to calibration.

Examining the results (figure 8) during the rapid rise in blood glucose from 100 to 140 mg/dl that was caused by the breakfast meal, there is no evidence of a lag in the NIR response compared to the Beckman blood glucose values. This tends to confirm that the unexpected lag in the prior data was due to causes other than the NIR measurement and therefore it may have medical significance.

In summary, I believe that the results of testing so far provide strong evidence for the expectation that NIR methods based on the device of U.S .patent application 08/385,073 can be applied to biomedical research and patient care, and could dramatically help in the treatment of diabetes. With the prevalence of diabetes increasing in the US to ~16 million by the end of the century, and considering that diabetes costs of over $100 billion per year account for 15% of our nation's health care budget, new treatment modalities could have enormous benefits.

I, Dr. Harry Shamoon, hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fines or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Harry Shamoon MD

Signature of Declarant

Nov 11, 1996.

Date

Harry Shamoon MD
Professor of Medicine
Department of Medicine and the Diabetes Research Center
Albert Einstein College of Medicine
1300 Morris Park Avenue, 701 Belfer
Bronx, NY 10461

Figure 1

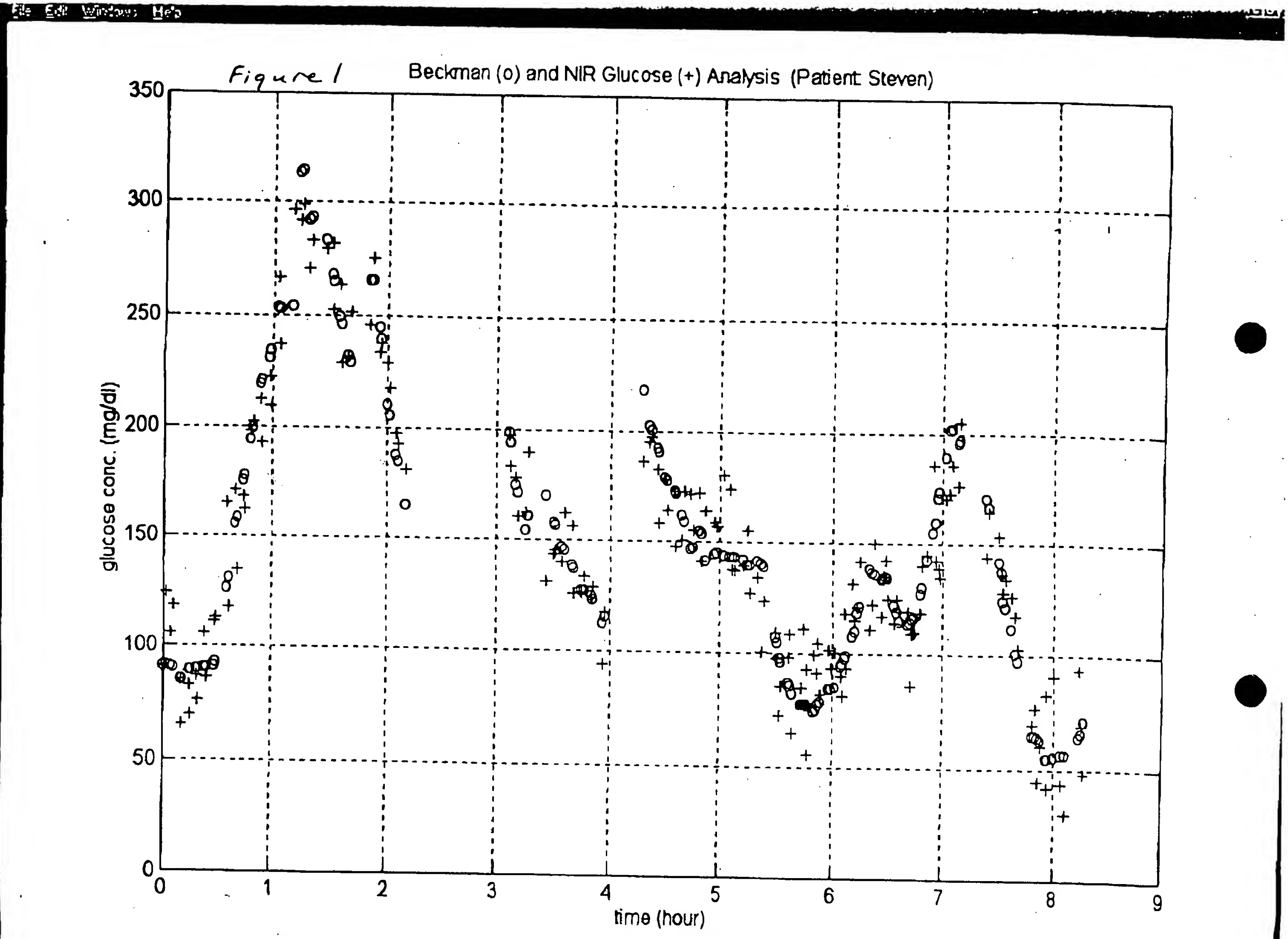
File Edit Window Help
Beckman (o) and NIR Glucose (+) Analysis (Patient: Steven)
glucose conc. (mg/dl)
350
300
250
200
150
100
50
0
time (hour)
0
1
2
3
4
5
6
7
8
9

Figure 2

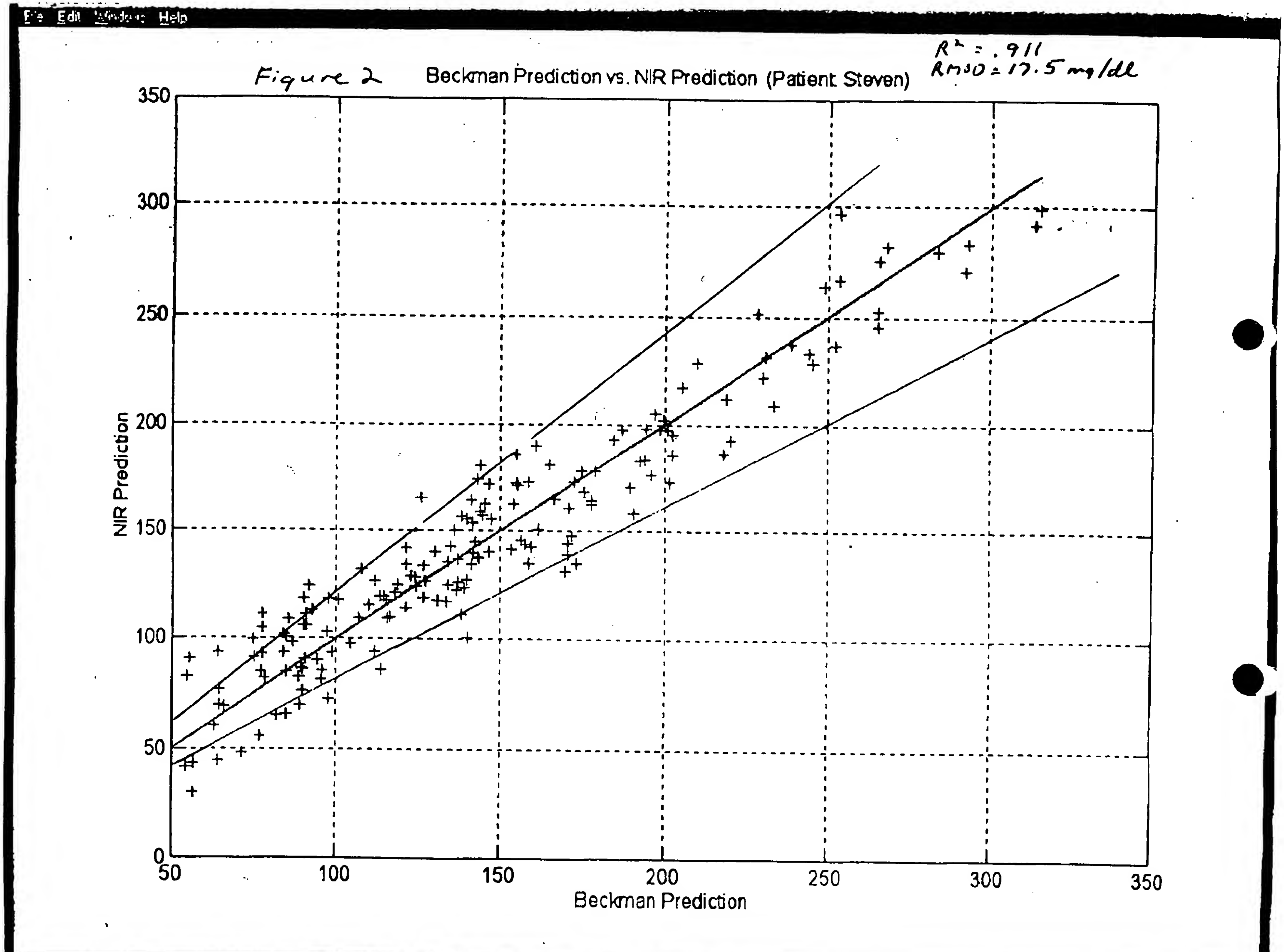
File Edit Window Help
Beckman Prediction vs. NIR Prediction (Patient Steven)
$R^2 = .911$
RMSD = 17.5 mg/dl
NIR Prediction
Beckman Prediction
0
50
100
150
200
250
300
350

Figure 3

NIR predicted dual ring vs. Beckman, R-sqr=0.887, RMSD=6.65 mg/dl, factors=20, N=128 (patient: Annmarie)

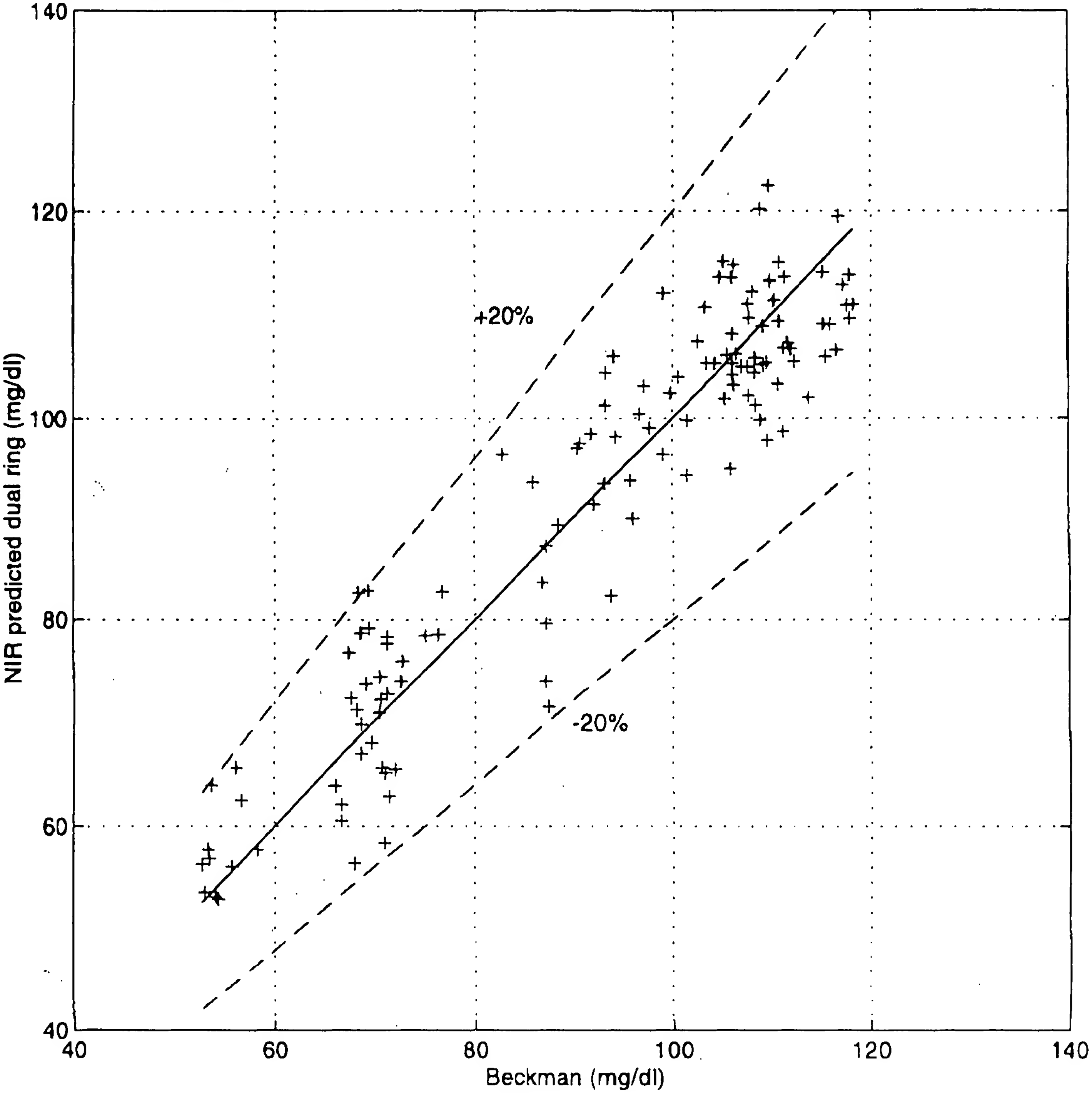

Figure 4

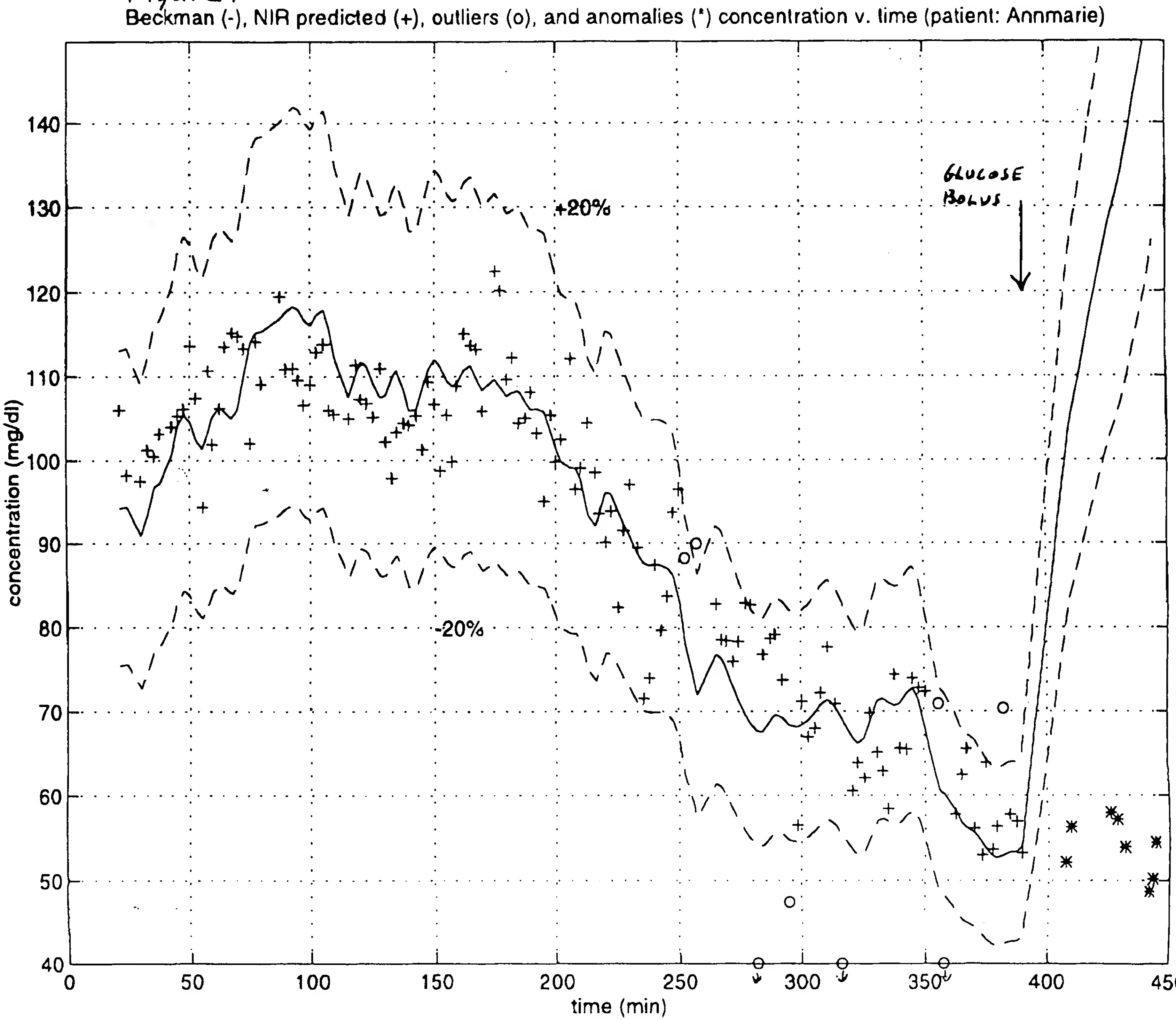
Beckman (-), NIR predicted (+), outliers (o), and anomalies (*) concentration v. time (patient: Annmarie)
concentration (mg/dl)
time (min)
+20%
-20%
GLUCOSE BOLUS
140
130
120
110
100
90
80
70
60
50
40
0
50
100
150
200
250
300
350
400
450

Figure 5

NIR predicted inner ring vs. Beckman, R-sqr=0.871, RMSD=7.11 mg/dl, factors=20, N=128 (patient: Annmarie)

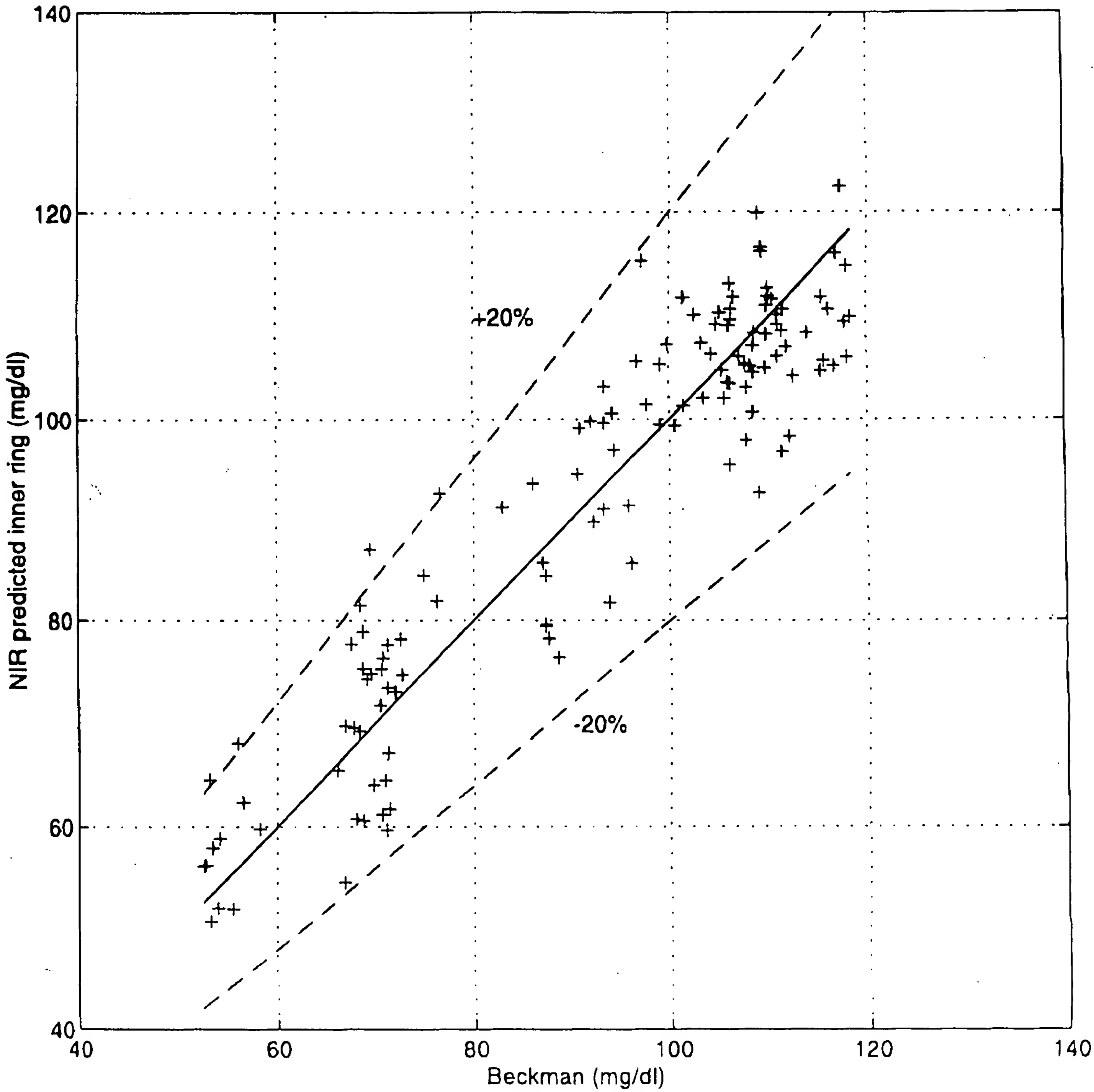

Figure 6

NIR predicted outer ring vs. Beckman, R-sqr=0.842, RMSD=7.89 mg/dl, factors=20, N=128 (patient: Annmarie)

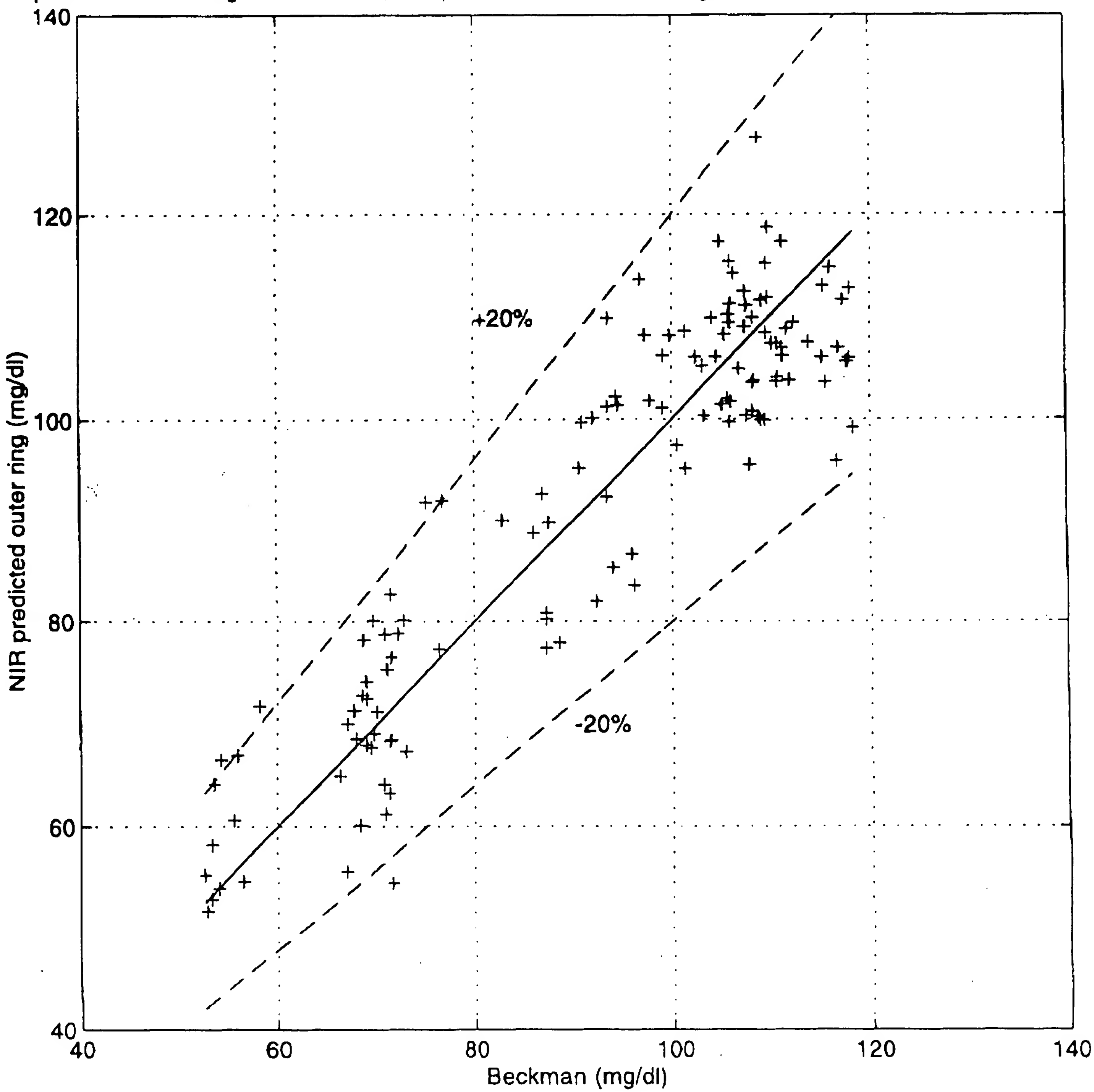

Figure 7

NIR predicted vs. Beckman, R-sqr=0.831, RMSD=8.59 (mg/dl), factors=24, N=177 (Annmarie and Dave Combined)

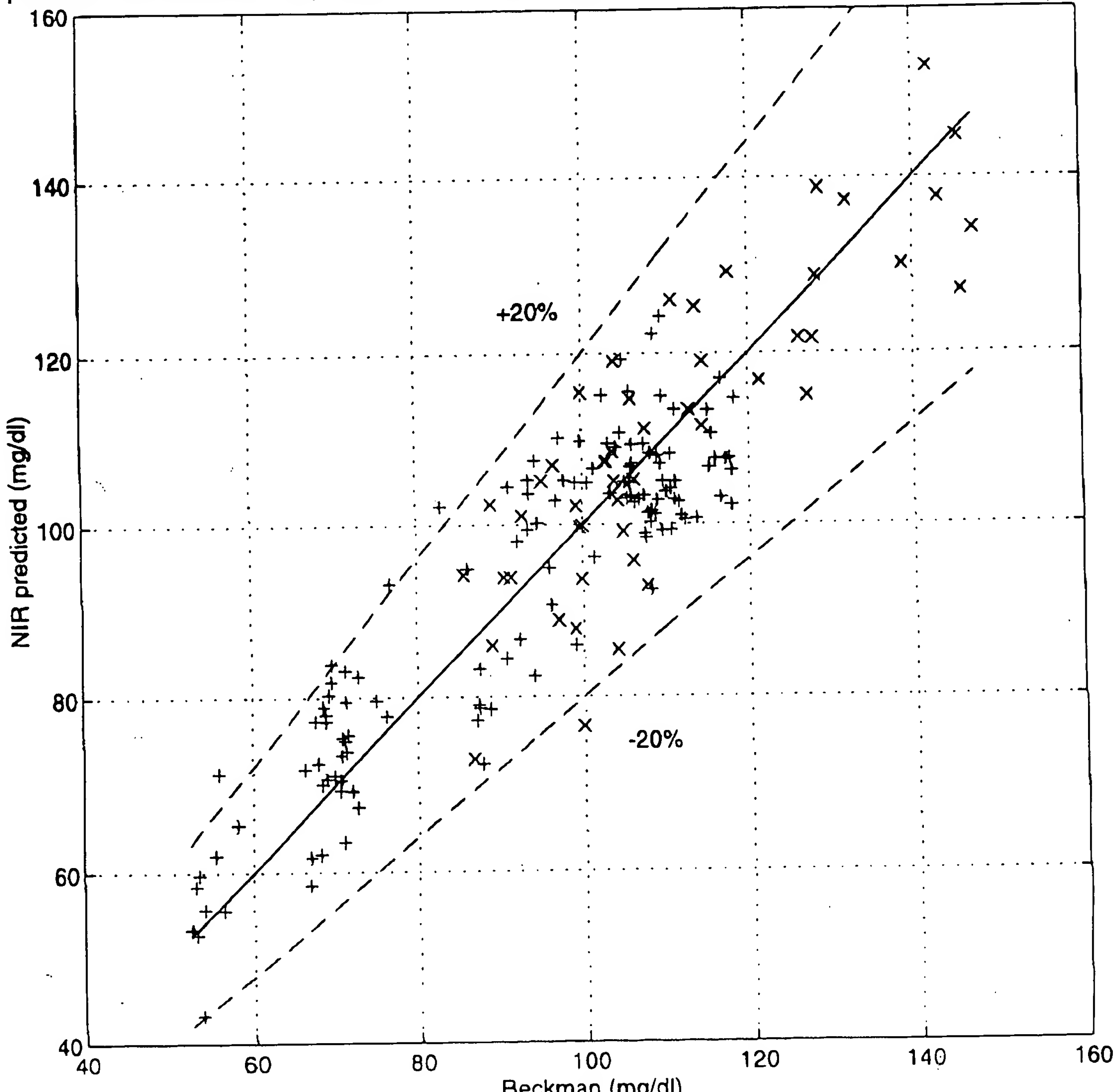

Figure 8 Beckman, NIR predicted (+), outliers (o) concentration vs. time (patient: Dave) Combined Calibration

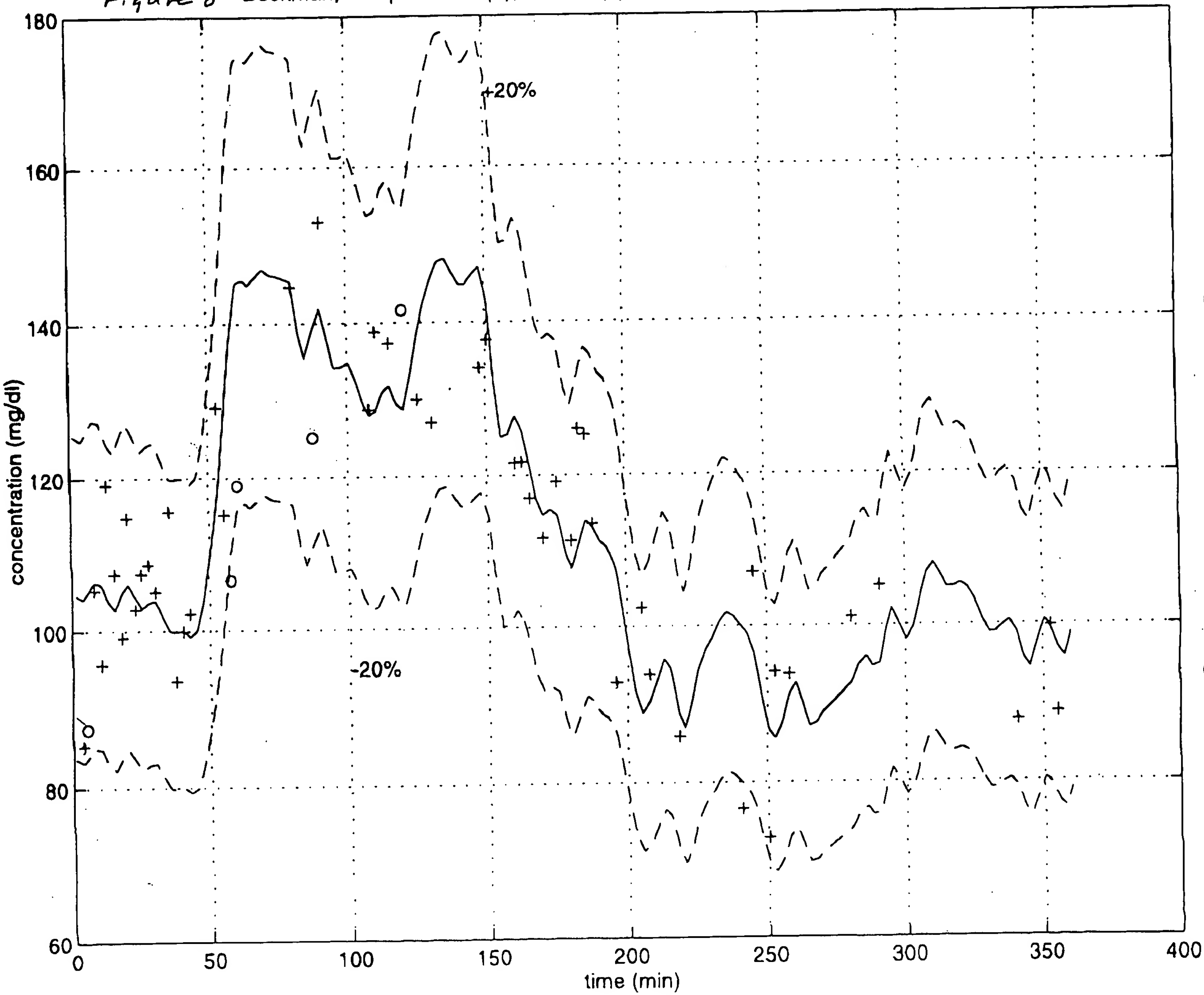

Exhibit 3

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXAMINER: R. ROSENBERGER : ATTY DOCKET: GK-BIO-292C2

APPLICANT(S): E.W. STARK : GROUP ART UNIT: 2505

SERIAL NO.: 08/385,073 : FILED 02/07/95

TITLE: METHOD AND APPARATUS FOR OPTICAL INTERACTANCE AND TRANSMITTANCE MEASUREMENTS

---oOo---

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132

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GROUP 2500

SIR:

I, Karl Norris, hereby declare the following:

I

I have received the Bachelor of Science in Engineering degree from Penn State University in 1942.

II

For more than 37 years I served as a research leader in the USDA Agriculture Research Service developing spectroscopic techniques for measuring the quality of agricultural products. I retired in 1988 as Director of the USDA, ARS, Instrumentation Research Laboratory. I, together with my associates, developed most of the techniques that are now being used for non-invasive spectroscopic measurements. Among these techniques were the pioneering use of near-infrared (NIR) diffuse transmittance, diffuse reflectance, and interactance combined with multiple linear regression and later chemometric techniques for the quantitative and qualitative determination of the composition and physical characteristics of scattering materials. These developments were published in more than 100 scientific papers that I authored or co-authored. As a result, I have received numerous awards, including the Alexander von Humboldt Award for developing NIR technology and the USDA Superior Service Award. I have also been elected a member of the National Academy of Engineering.

Since 1988 I have served as a consultant to industry on the design and application of near-infrared spectroscopic instrumentation. I have also been consulting on medical uses of this technology, particularly for measurement of the oxygen saturation of the brain.

III

I am familiar with the prior art devices which perform optical interactance and transmittance measurements. Specifically, I originally developed the techniques for "interactance" measurements including: 1) illuminating one area on the surface of a sample and measuring the diffuse transmitted light from another area of the sample surface; 2) using fiber optics to illuminate and collect diffusely reflected and transmitted light; and 3) using a single concentric detection ring surrounding a central source of illumination. I was co-author of a paper published in 1984 entitled "A new Approach for Estimation of Body Composition: Infrared Interactance", American Journal of Clinical Nutrition, Vol. 40, pp 1123-1130 which first described and named the interactance optical geometry. Since then, I have designed or studied the design of many such devices. I am also familiar with the work of Jobsis, Ferrari, Delpy, Hanley, and Chance in measuring the oxygen saturation of the brain by near-infrared spectroscopy.

The closest prior art devices are the fiber optic probes for use in contact with the surface of the sample which utilize separated illumination and detection areas to measure absorption within the sample. These all use a single source and a single detection means and therefore provide only one measurement. In many cases of interactance devices, a circular central aperture surrounded by a concentric ring aperture was used, one aperture for the source and the other for detection, in order to maximize the measurement volume for a given path length through the sample. In at least one case, a number of equally spaced parallel slit apertures were used, alternating between source and detection functions, in order to increase the measurement volume. There was still only one detection signal generated and all the parallel paths were of equivalent geometry. In other cases, the source and detection areas were placed on opposite sides of the sample to generate a diffuse transmittance measurement.

Diffuse reflectance, transmittance and interactance measurements made with these single measurement devices have significant problems and shortcomings. Surface effects are a major obstacle, particularly for reflectance where most of the detected signal arises at or very near the surface. The transmittance and interactance optical geometries are specifically designed to eliminate collection of the direct surface reflection. However, in each of these cases the illumination must pass through the portion of the sample near the surface. In many cases, particularly for in-vivo medical measurements, the surface portion of the sample is significantly different from the interior from which information is desired. The simple single source-single detection geometry provides no additional information for discrimination of the effects of the region near the surface from those of the deeper interior portion of the sample. Several investigators have proposed laser pulse time-of-flight or phase detection of very high frequency source modulation to isolate an interior measurement volume in the brain.

The depth of penetration and the path length of the measurement provided by interactance devices is related to the spacing between the source and detection areas. The effective path through the sample is the result of a complex combination of absorption and scattering effects occurring within the volume of the sample. In the simple single source-single detection devices, the depth of penetration and effective pathlength cannot be simultaneously optimized. Increased spacing between the source and detection apertures simultaneously increases the depth of penetration and the effective pathlength. Due to both scattering and absorption losses, increased pathlength rapidly reduces the detected energy and the measurement signal-to-noise ratio. Inhomogeneous samples further complicate the picture. For example, an inhomogeneity located near the central aperture is common to all of the paths through the sample. Consquently, it is unduly weighted in the measurement thereby increasing the error. Layered samples, like skin which is made up of many layers of tissue of different characteristics, provide additional problems. For example, the source energy may be preferentially guided by the structure resulting in systematic errors in the measurement. In essence, the measurement is not being made on the desired portion of the sample. A major shortcoming of the prior art measurement technology is the lack of optimization of the measurement volume. Furthermore, the physics of light transmission through absorbing and scattering media ensures that the resulting measured signal is highly nonlinear with respect to concentration and other properties of the sample that are to be determined.

I have also reviewed the optical geometries of the Borsboom, Hirao and Howarth patents which were cited by the examiner as prior art. Borsboom uses a central source fiber and at least one parallel detection fiber. In addition, he also measures the energy which is reflected or backscattered into the illumination fiber optics as a second detection site. However, this energy is predominately returned from the surface of the sample. It exhibits little or no absorption resulting from interaction with the interior volume of the sample. It appears that Borsboom has physically combined a reflectometer to measure backscatter with a classical single ring interactance probe to measure absorption. He does not cite combining the two measurements in any way to provide an improvement over the problems and shortcomings discussed in the paragraphs above. Furthermore, his second path cannot be adjusted to provide sufficient pathlength for obtaining the necessary absorption signal for use to cancel undesired portions of the absorption signal from the longer path. For this purpose, it is essential to have space between the source and detection areas in order to control the depth of penetration and the measurement volume encompassed by the effective optical path through the sample.

In his more detailed description and explanation, Borsboom refers to "Arranged in a ring ... are four juxtaposed optical fibers 7" while his figure 5 shows a full ring of fibers. There is no written discussion of any advantages of either a full or partial ring over a single juxtaposed detection fiber nor indication that such is a preferred embodiment of his device. In short, Borsboom provides no solutions to the problems listed above.

Hirao and Howarth both use a linear arrangement of source and detection apertures to provide two optical paths defined by one aperture common to the two paths and separate apertures at the other ends of the two paths. Hirao addresses the problems of sample

inhomogeneity and the positional deviations of the measurement apparatus which deteriorate the reproducibility of the result. He apparently wishes to measure a small homogeneous region within the larger heterogeneous material. He uses either one detector and a plurality of sources or a single source and a plurality of detectors to make the measurements. Hirao desires to obtain a commonality of path over the majority of the distance from each measurement point to the common detector or source point. His approach is to obtain information from a very small region in the vicinity where the paths are not common by cancelling the signal common to both paths. His figures 2 and 4 indicate that he does not appreciate the depth of penetration and lateral diffusion differences between the two paths Not withstanding this, his examples 1 and 2 show that the distances from source to receiver are almost the same for the two paths and substantially longer (3 to 6 cm) than the difference in these distances (0.3 to 0.5 cm). This 10:1 ratio of spacing maximizes the commonality of path. Hirao also spaces the pair of apertures defining the measurement volume far from the common aperture so as to avoid the surface effects near the common point. His optical geometry is designed for the measurement of small homogeneous regions of the overall sample and it requires measurement of the small absorption difference between two paths, each of which exhibits high absorption because it must be substantially longer than the path difference which defines the small volume of interest. Use of extended apertures, such as rings, would prohibit such a measurement.

Howarth is concerned with two measurements, the bulk reflectance and the consistency, of paper pulp. The bulk reflectance is measured using the visible wavelength range for sample and the near-infrared range for reference. This measurement is made using a single source aperture and a single detection aperture spaced in the direction of flow of the pulp in order to reduce the effects of consistency variation, pitch buildup on windows, and the boundary layer which adversely affect simple reflectance measurements through a single window. In order to reduce pulp noise, Howarth's apertures are made fully diffusing so that there is no optical directionality of the light within the sample caused by the angle at which the sources or detectors are placed relative to the window. Howarth indicates that the source to detector spacing should be sufficient so that most of the optical paths pass through material that is outside the boundary layer however, every path still includes boundary layer material which is included in the measurement. His reduction in undesired effects results from changing from the reflectance optical geometry to a simple prior art interactance configuration. Howarth also shows that the spacing may be varied to minimize the sensitivity of the bulk reflectance measurement to consistency of the pulp.

Howarth discloses that by using a larger spacing than optimum for bulk reflectance measurements, consistency could also be measured using the above optical geometry. The facts that he uses a single wavelength to measure consistency, that brown and bleached stock have equal response, and that the measurement could not be made if an additional scatterer such as clay or titanium dioxide was added to the pulp indicates that scattering is the basis of the consistency measurement . In order to reduce the effects of pitch and dirt on the windows and pulp noise on this consistency measurement, Howarth states that it is preferred to measure the ratio of received radiation in at least two different window locations. The second window is spaced further from the source than the distance which provides minimum consistency sensitivity

therefore use of this ratio measurement for the bulk reflectance measurement would increase the pulp noise and decrease the accuracy and precision. He provides no discussion of other advantages of such an arrangement and nor does he suggest that it might improve the bulk reflectance measurement, which depends on absorption within the sample rather than only scattering. Thus, the use of a second window and measurement channel was primarily directed to the issue of dirt buildup affecting a scattering measurement in a particular environment. In most cases, there are many approaches to solving this problem more economically and effectively than adding a second channel, for example, the use of a protective film over the measurement tip as suggested by Borsboom.

Howarth does not address depth of penetration, layered and inhomogeneous samples, lateral spreading of the light, or optimizing the effective measurement volume for this single source - two detector configuration. The linear arrangement of source and detectors is far from optimum in maximizing the effective measurement volume while controlling the depth of penetration. Thus it is clear that Howarth did not appreciate the problems solved by the invention of US Patent Application 08/385,073.

In overall summary of the prior art, Borsboom does no more than disclose the basic interactance optical geometry described in the application specification as prior art . For the reasons stated above, neither Hirao nor Howarth disclose any teaching which would lead an individual skilled in the art to the invention made by applicant.

IV

Transmittance and interactance spectroscopy provides a powerful technique for non-invasive measurements on a very wide range of possible samples, but we have not had an optimized geometry for measurements on the human body. The major obstacles have been surface effects, non-linearity, uncontrolled optical path, sample inhomogeneity, and signal-to-noise ratio. There is a long felt need for a device that would reduce or overcome the problems of the prior art devices. In order to reduce the effects of sample inhomogeneity, such a device would maximize the measurement volume for a predetermined aperture spacing and avoid preferentially measuring any region of the sample. . It would control the effective depth from which the measurement is made in order to measure the desired stratum of the sample while reducing surface effects. It would define and limit the effective optical paths within the sample and thereby reduce and stabilize the non-linearity. Finally, it would maximize the optical throughput for both the source and detection functions in order to maximize the signal-to-noise ratio of the measurement.

V

I have reviewed measurements presented in a Declaration executed by Dr. Harry Shamoon which were produced by a device described and shown in US Patent Application No. 08/385,073. These measurements show very promising results in predicting glucose content

of the blood of patients using a new spectrometer incorporating this device. The quality of the measurements indicates that the device provides a significant and unexpected improvement over the prior art devices discussed above. Based on my knowledge of the device geometry, I believe that the dual ring geometry and signal processing has controlled the effective measurement depth thereby substantially reducing the effects of the surface and the layered nature of the human body skin. The symmetry of the device has produced concentric measurement volumes that reduce the effects of lateral spreading of the effective paths, including non-linearity. Each of the measurement volumes is as large as possible for the predetermined spacing of the rings and the signal from the region of the central aperture is cancelled. Both factors are effective in reducing the effects of sample inhomogeneity. In addition, directing the light toward the central aperture has increased the energy density at the detection area compared to the prior art devices, thereby enhancing the signal-to-noise ratio of the measurement.

Finally, the signal-to-noise ratio of the measurements is enhanced by using the rings, with their greater area, as the sources rather than the smaller central aperture. The high numerical aperture and large area of source fibers can readily be filled using a tungsten projector lamp with integral reflector thereby maximizing the energy introduced into the sample. This maximizes the energy density scattered into the detection aperture. The detection area and numerical aperture are limited by the requirements of the spectrometer. However, a small detection area allows use of a small detector. Since the detector noise is proportional to the square root of its area, the small detector area is less of a penalty for signal-to-noise ratio than simple throughput considerations might indicate. A system that uses a monochrometer source with limited throughput at the central aperture and detection through the ring apertures using large area detectors would have significantly poorer performance.

For all the reasons stated above, I believe that the device disclosed in US Patent Application 08/385,073 is a significant and unique improvement over the prior art.

I, Karl Norris, hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fines or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon..

Karl H. Norris
Signature of Declarant
Nov. 17, 1996
Date

I hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, DC 20231, on the date listed below.

Signature [signature] Date 18 Nov 96

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXAMINER:	R. ROSENBERGER	: ATTY DOCKET NO.:	GK-BIO-292C2
APPLICANT(S):	E. W. STARK	: GROUP ART UNIT:	2505
SERIAL NO.:	08/385,073	: FILED:	02/07/95
TITLE:	METHOD AND APPARATUS FOR OPTICAL INTERACTANCE AND TRANSMITTANCE MEASUREMENTS		

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Assistant Commissioner for Patents
Washington, D.C. 20231

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR §1.136

SIR:

Pursuant to 37 CFR § 1.136, applicants hereby petition for a three month extension-of-time to extend the statutory response period for the Office Action dated May 16, 1996, to November 18, 1996. A check covering the statutory fee of $930 is attached. The Commissioner is authorized to charge Deposit Account No. 13-0025 with any additional fees under 37 CFR § 1.16 or § 1.17 necessary to keep this application pending in the United States Patent and Trademark Office.

Respectfully submitted,
McAULAY FISHER NISSEN GOLDBERG & KIEL, LLP

[signature: Gerald H. Kiel]

Gerald H. Kiel
Reg. Number: 25,116
Telephone: 212-986-4090
Facsimile: 212-818-9479

I hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, DC 20231, on the date listed below.

18 Nov 96

Signature

Date

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXAMINER:	R. ROSENBERGER	: ATTY DOCKET NO.:	GK-BIO-292C2
APPLICANT(S):	E. W. STARK	: GROUP ART UNIT:	2505
SERIAL NO.:	08/385,073	: FILED:	02/07/95
TITLE:	METHOD AND APPARATUS FOR OPTICAL INTERACTANCE AND TRANSMITTANCE MEASUREMENTS		

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Assistant Commissioner for Patents
Washington, D.C. 20231

NOTICE OF APPEAL

SIR:

Applicant hereby appeals to the Board of Patent Appeals and Interferences from a decision dated May 16, 1996 of the Examiner to finally reject claims 1, 6-7, 33-34, 36-42, and 54-55. A petition for a three month extension-of-time to respond to the final rejection is being filed by applicant concurrently with this notice of appeal. A check covering the extension-of-time fee of $930 and the appeal fee of $300 is attached. The Commissioner is authorized to charge Deposit Account No. 13-0025 with any additional fees under 37 CFR § 1.16 or § 1.17 which may be necessary to keep this application pending in the United States Patent and Trademark Office.

Respectfully submitted,
McAULAY FISHER NISSEN GOLDBERG & KIEL, LLP

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